

## Interaction between respiration and right versus left ventricular volumes at rest and during exercise: a real-time cardiac magnetic resonance study

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<sup>1</sup>Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium; <sup>2</sup>Department of Cardiovascular Imaging and Dynamics, University of Leuven, Leuven, Belgium; <sup>3</sup>Department of Pneumology, University Hospitals Leuven, Leuven, Belgium; <sup>4</sup>Department of Radiology, University Hospitals Leuven, Leuven, Belgium; and <sup>5</sup>St Vincent's Hospital Department of Medicine, University of Melbourne, Fitzroy, South Australia, Australia

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**Claessen G, Claus P, Delcroix M, Bogaert J, Gerche AL, Heidbuchel H.** Interaction between respiration and right versus left ventricular volumes at rest and during exercise: a real-time cardiac magnetic resonance study. *Am J Physiol Heart Circ Physiol* 306: H816–H824, 2014. First published January 24, 2014; doi:10.1152/ajpheart.00752.2013.—Breathing-induced changes in intrathoracic pressures influence left ventricular (LV) and right ventricular (RV) volumes, the exact nature and extent of which have not previously been evaluated in humans. We sought to examine this “respiratory pump” using novel real-time cardiac magnetic resonance (CMR) imaging. Eight healthy subjects underwent serial multislice real-time CMR during normal breathing, breath holding, and the Valsalva maneuver. Subsequently, a separate cohort of nine subjects underwent real-time CMR at rest and during incremental exercise. LV and RV end-diastolic volume (EDV) and end-systolic volume (ESV) and diastolic and systolic eccentricity indexes were determined at peak inspiration and expiration. During normal breathing, inspiration resulted in an increase in RV volumes [RVEDV:  $+18 \pm 8\%$ , RVESV:  $+14 \pm 12\%$ , and RV stroke volume (SV):  $+21 \pm 10\%$ ,  $P < 0.01$ ] and an opposing decrease in LV volumes ( $P < 0.0001$  for interaction). During end-inspiratory breath holding, RV SV decreased by  $9 \pm 10\%$  ( $P = 0.046$ ), whereas LV SV did not change. During the Valsalva maneuver, volumes decreased in both ventricles (RVEDV:  $-29 \pm 11\%$ , RVESV:  $-16 \pm 14\%$ , RV SV:  $-36 \pm 14\%$ , LVEDV:  $-22 \pm 17\%$ , and LV SV:  $-25 \pm 17\%$ ,  $P < 0.01$ ). The reciprocal effect of respiration on LV and RV volumes was maintained throughout exercise. The diastolic and systolic eccentricity indexes were greater during inspiration than during expiration, both at rest and during exercise ( $P < 0.0001$  for both). In conclusion, ventricular volumes oscillate with respiratory phase such that RV and LV volumes are maximal at peak inspiration and expiration, respectively. Thus, interpretation of RV versus LV volumes requires careful definition of the exact respiratory time point for proper interpretation, both at rest and during exercise.

respiration; cardiac volumes; cardiac magnetic resonance imaging; exercise; Valsalva

THE INFLUENCE OF RESPIRATION on cardiac output is well recognized but frequently overlooked. Although a reduction in left ventricular (LV) stroke volume (SV) during inspiration has been repeatedly observed (5, 6, 16, 18, 20), most contemporary studies that include the quantification of SV seem to ignore the confounding influence of respiration. Moreover, an invasive study (20) in animals has suggested that the respiratory phase

exerts opposing effects on the SV of the LV and right ventricle (RV), and yet many cardiac imaging studies have incorrectly used equality of ventricular SVs as a measure of accuracy (2, 12, 22, 28).

In humans, the interactions between respiration and cardiac function have been difficult to evaluate. Until recently, it has not been possible to simultaneously assess biventricular volumes in real time throughout the respiratory cycle using non-invasive techniques. The most commonly used nuclear and magnetic resonance imaging techniques use cardiac gating across multiple cardiac cycles to obtain adequate spatial resolution. However, such a technique means that the effects of respiration are averaged and therefore ignored. Recently, we and others (9, 12, 13, 17) have described a novel cardiac magnetic resonance (CMR) imaging technique in which images are acquired in real time throughout normal respiration, exercise, and other physiological maneuvers. This methodology provides a new opportunity to assess the pattern and magnitude of the influence of respiration on cardiac volumes in humans.

The reason for assessing cardiorespiratory interaction is twofold: 1) because it is likely that oscillatory intrathoracic pressures aid cardiac filling and output (the so-called “respiratory pump”) and 2) to quantify the potential errors produced in imaging studies that use the assumption of biventricular SV equivalence as a measure of accuracy.

We hypothesized that real-time CMR quantification of biventricular volumes acquired throughout respiration would enable us to elucidate the nature and extent of the cardiorespiratory interaction. We aimed to 1) assess the effects of respiration on instantaneous biventricular volumes during normal respiration and exaggerated respiratory maneuvers and 2) assess whether these cardiopulmonary interactions persisted during the high-flow states of intense exercise.

### METHODS

The study protocol was divided into two parts: 1) a respiratory maneuver protocol in which LV and RV volumetric responses to normal breathing, end-inspiratory breath holding, and the Valsalva maneuver were compared and 2) an exercise CMR protocol in which the effects of respiration on biventricular volumes were assessed at rest and during supine exercise.

The study protocol conformed with the Declaration of Helsinki and was approved by the local ethics committee. All patients provided informed consent.

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### Subjects

Eight healthy subjects (all men, age:  $29 \pm 5$  yr) volunteered to participate in the respiratory maneuver protocol. All participants performed some regular exercise, and six participants were competitive athletes.

A separate cohort of nine volunteers (8 men, age:  $35 \pm 12$  yr) participated in the exercise CMR protocol. All subjects performed some regular exercise, and five subjects were competitive athletes.

### Study Protocol

**Respiratory maneuver protocol.** Subjects underwent real-time CMR imaging during normal breathing, end-inspiratory breath holding, and a Valsalva maneuver while lying within the CMR bore. First, images were acquired during spontaneous regular respiration and then during a single inspiratory breath hold of  $\sim 20$ -s duration. For the Valsalva maneuver, subjects were asked to perform a forced expiration against a closed glottis with image acquisition commencing immediately and lasting  $\sim 20$  s.

**Exercise CMR protocol.** The exercise CMR protocol consisted of cardiopulmonary testing and exercise CMR. Cardiopulmonary testing was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) using an incremental protocol commencing at 50 W and increasing progressively (25 W/min) until exhaustion. This test was used to standardize exercise prescription for the CMR protocol, which was undertaken the following day. For the CMR study, subjects performed exercise within the CMR bore on a supine cycle ergometer with adjustable electronic resistance (Lode, Groningen, The Netherlands). Images were acquired during free breathing at rest and then at 25%, 50%, and 66% of the maximal power wattage as determined by the cardiopulmonary testing on the previous day. We have previously demonstrated that 66% of the maximal upright exercise power (in W) corresponded to the maximal sustainable exercise intensity in the supine position. These workloads will subsequently be referred to as rest, low, moderate, and maximal intensity. Each stage of exercise was maintained for  $\sim 3$ –4 min (1 min to achieve a physiological steady state and 2–3 min for image acquisition).

### CMR Equipment and Image Acquisition and Analysis

The real-time CMR protocol used for this study has been comprehensively described and validated against invasive standards (9).

Furthermore, we (9) have previously demonstrated excellent interobserver ( $R = 0.98$  and  $R = 0.97$  for LV and RV SV, respectively) and interstudy reproducibility ( $R = 0.98$  for cardiac output) using this technique. In brief, images were acquired using a Philips Achieva 1.5-T CMR with a five-element phased-array coil (Philips Medical Systems, Best, The Netherlands). Steady-state free precession cine imaging was performed without cardiac gating. Imaging parameters were as follows: field of view,  $320 \times 260$  mm (approximately);  $128 \times 128$  matrix; flip angle,  $50^\circ$ ; SENSE factor, 2 (Cartesian  $k$ -space undersampling); repetition time, 1.8 ms; echo time, 0.9 ms; and reconstructed voxel size,  $2.3 \times 2.3 \times 8$  mm.

A three-dimensional stack of 13–18 contiguous 8-mm image slices, covering both ventricles from the apex to base, was serially acquired in the short-axis (SAX) plane (Figs. 1 and 2) and subsequently in the horizontal long-axis (HLA) plane. At rest, each slice level consisted of 100 consecutive image frames in the SAX plane and 80 consecutive frames in the HLA plane. All image frames were acquired during free breathing with a temporal resolution of 36–38 ms. The required acquisition time per slice level in the SAX plane was  $\sim 3.8$  s (100 frames  $\times$  38 ms/frame) at rest. Subjects were asked to breathe regularly in and out during image acquisition, such that at least one complete respiratory cycle was acquired per image slice. During breath holding and the Valsalva maneuver, the number of frame repetitions was reduced to 30 frames/slice level such that all image slices in the SAX plane could be acquired within 1 breath hold of  $\sim 16$ - to 21-s duration (30 frames  $\times$  38 ms/slice  $\times$  14–18 slices). Subsequently, all image slices were acquired during a second breath hold of  $\sim 20$  s for the HLA plane. For the exercise CMR protocol, a reduced number of repetitions (from 100 frames at rest to 60 frames/slice at maximal-intensity exercise) were programmed for each increase in exercise intensity, but there was sufficient time to acquire numerous cardiac cycles and at least one complete respiratory cycle at each slice of the cine acquisition.

Simultaneous with the image acquisition, information on the timing of respiration was obtained by measuring abdominal pressure with a plethysmograph placed on the upper abdomen, and electrocardiographic R-wave determination was derived from a hemodynamic monitor (Maglife Serenity, Schiller, Baar, Switzerland). These physiological data were retrospectively synchronized with the images using an in-house-developed software program (RightVol, Leuven, Belgium) such that contouring could be performed at a specified point of the respiratory cycle for all slices, as previously described (9).

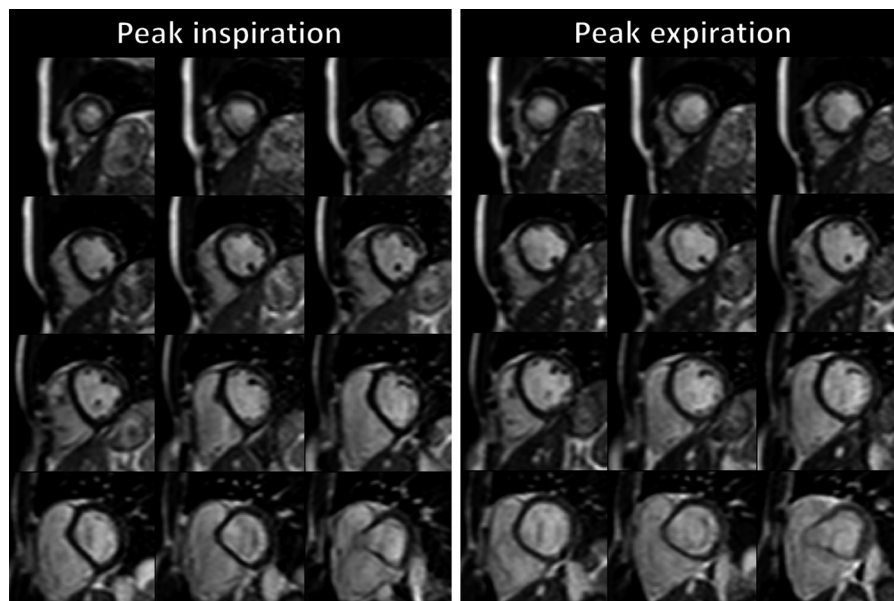
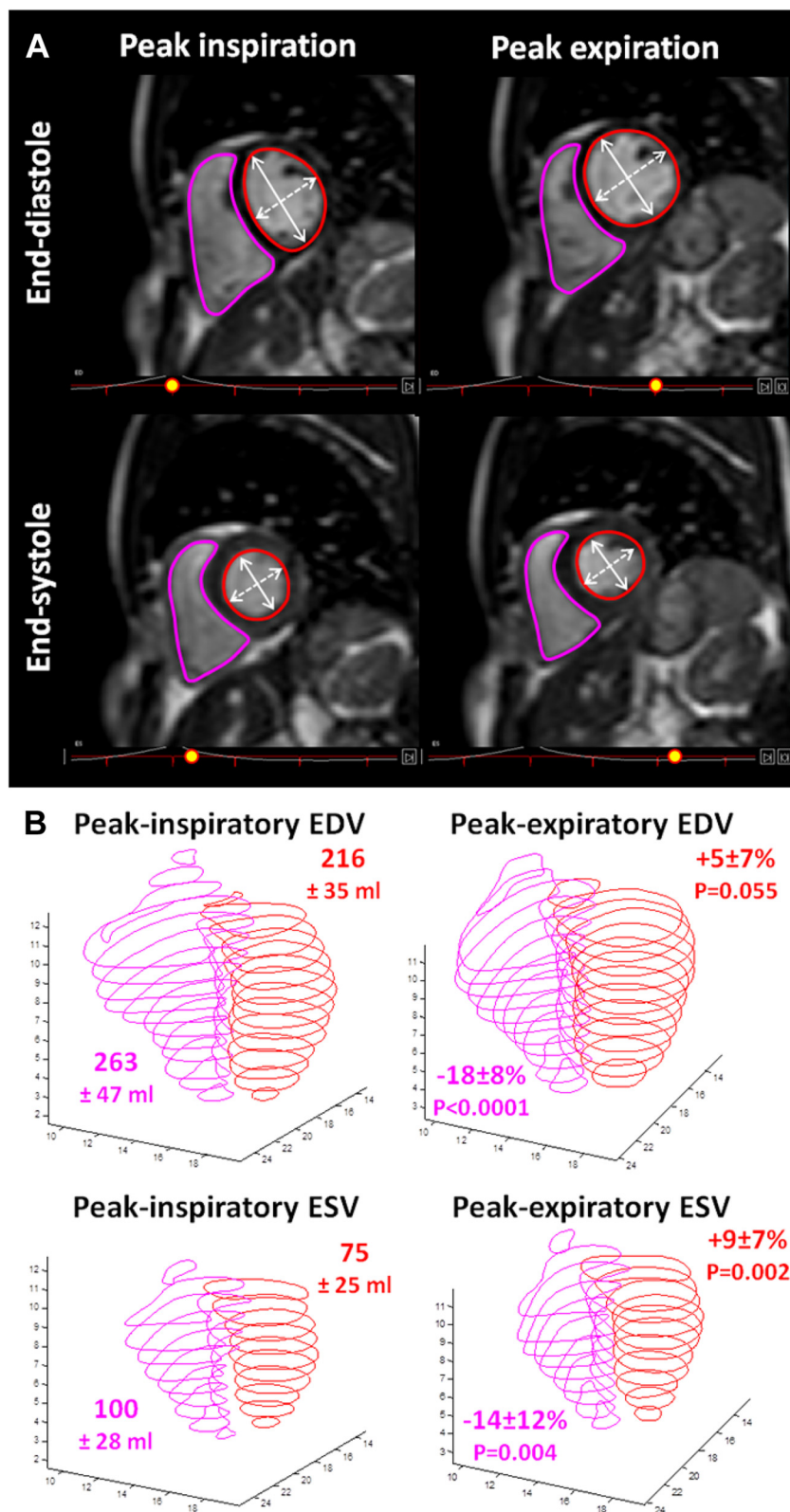


Fig. 1. Illustration of “raw cardiac magnetic resonance (CMR) data” at end diastole for each slice level, both at peak inspiration (*left*) and at peak expiration (*right*). It can be noted that right ventricular (RV) and left ventricular (LV) end-diastolic dimensions are maximal at peak inspiration and peak expiration, respectively. The increase in RV end-diastolic dimensions at peak inspiration is associated with a flattening of the septum, which can be appreciated at each slice level.

Fig. 2. Illustration of the cardiorespiratory interaction during normal breathing. In a representative midventricular short-axis slice (A), LV (red traces) and RV (pink traces) endocardial contours were manually traced at peak inspiration (left) and at peak expiration (right). Endocardial contours at each slice level were summed to derive the ventricular volumes as represented by the three-dimensional model of summed discs (B). The solid and dashed arrows depict the LV anteroposterior diameters and LV septolateral diameters, respectively. The eccentricity index was defined as the ratio of the anteroposterior to the septolateral diameter determined in a single midventricular slice. The physiological data can be seen immediately below each image in A. The red trace represents the electrocardiographic R wave, whereas the white trace represents the plethysmograph data, whereby an upward deflection represents inspiration. The yellow dot on this trace represents the point in time that the images were acquired. As can be seen in the images acquired during diastole, the yellow dot falls on the R wave compared with systole, where it falls after the R wave. For peak inspiratory images, the yellow dot corresponds with the maximal upward deflection of the plethysmograph trace, whereas for peak expiration it coincides with the nadir of the plethysmograph trace. EDV, end-diastolic volume; ESV, end-systolic volume.



At each slice level, peak inspiration and peak expiration were defined as the point at the top and bottom of the plethysmograph trace (i.e., maximal and minimal diaphragmatic excursion), respectively. For peak inspiration, we consistently selected the end-diastolic phase (identified as the largest ventricular blood area) that was closest to

(but before) peak inspiration, and we then selected the smallest blood pool area from the same cardiac cycle as the end-systolic frame (which usually fell just after peak inspiration). This was then repeated for peak expiration. LV and RV endocardial contours were manually traced on the SAX end-diastolic and end-systolic frames with simul-



taneous reference to the HLA plane, thus enabling the single analyzer (G. Claessen) to confirm the position of the atrioventricular plane. Trabeculations and papillary muscles were considered part of the ventricular blood pools. By a summation of disks, total end-diastolic volume (EDV) and end-systolic volume (ESV) were then calculated automatically for each ventricle by the software. First, all measurements were performed in all subjects at peak inspiration, and, subsequently, all measurements were repeated at peak expiration. SV was measured as the difference between EDV and ESV, and ejection fraction (EF) was calculated as SV divided by EDV. Mean EDV, ESV, SV, and EF during normal breathing were calculated as the average of the peak-inspiratory and peak-expiratory values.

After the volume analysis had been completed, a single midventricular slice in the SAX plane was used to calculate the eccentricity index, which was defined as the ratio of anteroposterior to septolateral diameters. This was calculated at end diastole and end systole during peak inspiration and peak expiration.

#### Statistical Analysis

Normal Gaussian distribution of all continuous variables was confirmed using a Kolmogorov-Smirnov test, and values are reported as means  $\pm$  SD throughout the text. Repeated-measures ANOVA was used to evaluate the effects of normal breathing, breath holding, and the Valsalva maneuver on biventricular volumes with the respiratory condition as a within-subject factor. The changes in EDV, ESV, and SV that occurred during the different respiratory conditions were expressed as percentages of the mean values during normal breathing, calculated as the average of peak-inspiratory and peak-expiratory values. The difference between LV and RV SV for each respiratory condition was compared using a paired sample *t*-test. For normal breathing, LV and RV SV were calculated as the average of peak-

inspiratory and peak-expiratory values. The influence of breathing upon biventricular volumes during the exercise CMR protocol was evaluated using repeated-measures ANOVA with exercise intensity and respiratory phase as within-subject effects. Diastolic and systolic eccentricity indexes at peak inspiration and peak expiration were compared using repeated-measures ANOVA with exercise intensity and respiratory phase as within-subject effects. The overall effect of respiration over the different exercise intensities is referred to as the main effect.

## RESULTS

### Respiratory Maneuver Protocol

Normal inspiration affected the ventricles in an opposing manner ( $P < 0.0001$  for interaction) with an increase in RV volumes and a decrease in LV volumes (Figs. 1–3). From peak expiration to peak inspiration, RVEDV increased by  $18 \pm 8\%$  ( $P < 0.0001$ ) and RVESV by  $14 \pm 12\%$  ( $P = 0.004$ ), resulting in a significant increase in RV SV at peak inspiration ( $+21 \pm 10\%$ ,  $P = 0.001$ ). LV changes opposed those of the RV, and the magnitude of the change was more modest. At peak expiration, LVESV increased by  $9 \pm 7\%$  ( $P = 0.002$ ), whereas the changes in LVEDV ( $+5 \pm 7\%$ ,  $P = 0.055$ ) and LV SV ( $+4 \pm 10\%$ ,  $P = 0.28$ ) were not significant. Changes in EDV and SV were significantly larger for the RV compared with the LV ( $P = 0.02$  for both). Mean LV SV (the average of peak inspiration and expiration) was not significantly different from mean RV SV ( $144 \pm 20$  vs.  $148 \pm 27$  ml,  $P = 0.35$ ). LV EF

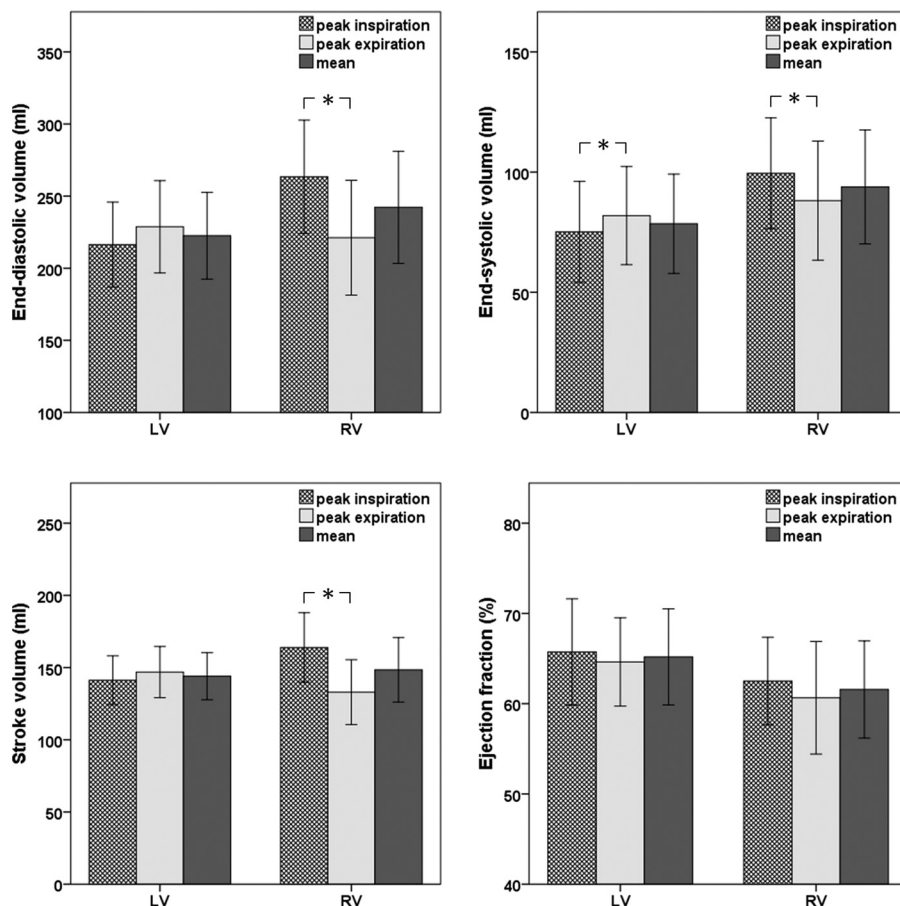
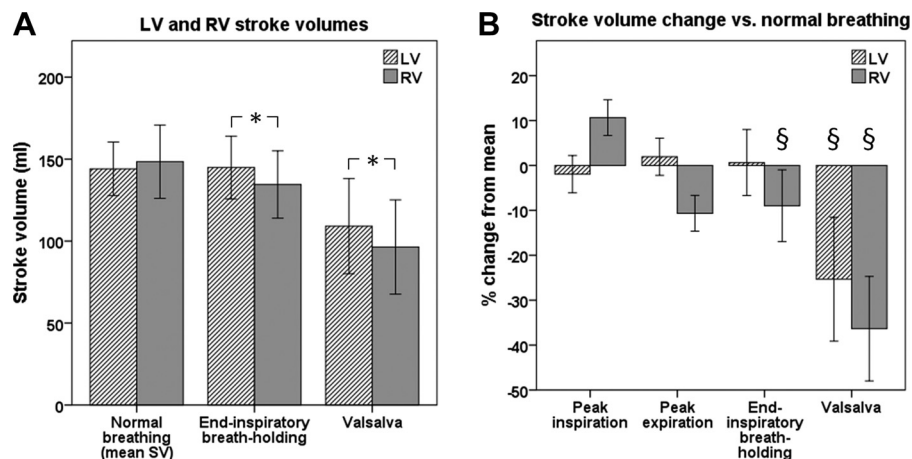


Fig. 3. Influence of normal breathing on biventricular volume measures. At peak inspiration, the fall in intrathoracic pressure increases venous return, right heart filling, and RV stroke volume (SV), resulting in an increase of flow into the pulmonary circulation. As intrathoracic pressure increases at peak expiration, the reduction in venous return and ventricular interaction result in diminished RV filling and output, whereas LV filling and output are preserved. Averaged over peak inspiration and peak expiration, LV and RV SVs are similar. \*Statistically significant differences between inspiration and expiration ( $P < 0.05$  by a paired samples *t*-test).

Fig. 4. A: agreement between LV and RV SV during normal breathing, breath holding, and the Valsalva maneuver. \*Statistically significant differences between LV and RV SV ( $P < 0.05$  by a paired samples  $t$ -test). For normal breathing, LV and RV SV are the average of peak-inspiratory and peak-expiratory values. B: changes in SV during normal breathing, breath holding, and the Valsalva maneuver. LV and RV SVs during peak inspiration, peak expiration, end-inspiratory breath holding, and the Valsalva maneuver were compared with mean LV and RV SVs during normal breathing (average of peak inspiration and peak expiration).  $\$P < 0.05$  by repeated-measures ANOVA.



and RV EF did not change during normal breathing ( $P = 0.22$  and  $P = 0.87$ , respectively).

Compared with normal breathing, RV SV decreased during breath holding ( $-9 \pm 10\%$ ,  $P = 0.046$ ) and more profoundly during the Valsalva maneuver ( $-36 \pm 14\%$ ,  $P < 0.0001$ ; Fig. 4). The total decrease in RV SV with the Valsalva maneuver was due to a  $29 \pm 11\%$  decrease in RVEDV (Fig. 5), whereas RVESV only decreased by  $16 \pm 14\%$ . RV EF did not differ between normal breathing and breath holding ( $P = 0.22$ ) but decreased significantly during the Valsalva maneuver com-

pared with normal breathing ( $54.9 \pm 7.6$  vs.  $61.6 \pm 6.4\%$ ,  $P = 0.01$ ). In contrast to the RV volume changes, LVEDV, LVESV, and LV SV were similar between normal breathing and breath holding ( $P = 0.43$ ,  $P = 0.62$ , and  $P = 0.87$ , respectively). However, during the Valsalva maneuver, there was a significant decrease in LVEDV ( $-22 \pm 17\%$ ,  $P = 0.009$ ) and LV SV ( $-25 \pm 17\%$ ,  $P = 0.003$ ). LV EF did not change significantly between the different respiratory maneuvers ( $P = 0.26$ ). The changes in EDV and SV with the Valsalva maneuver were more profound for the RV than for the

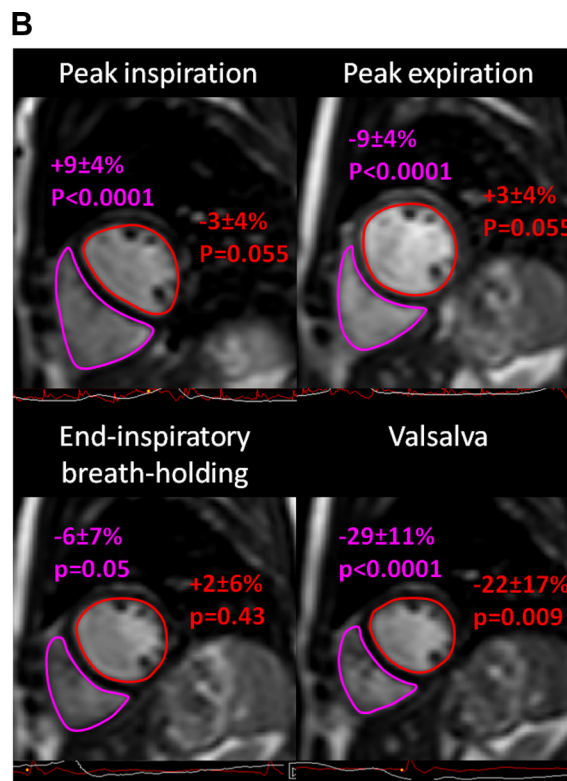
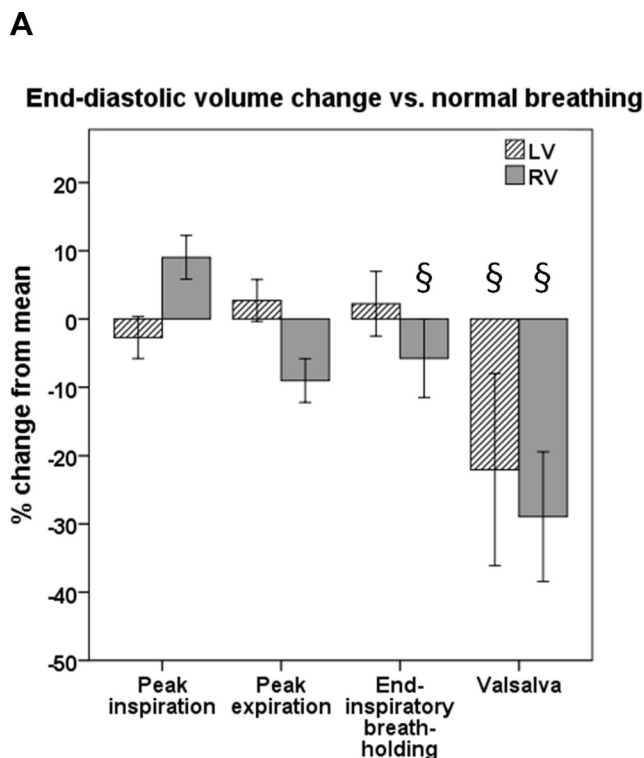


Fig. 5. Changes in EDV during normal breathing, breath holding, and the Valsalva maneuver. A: LVEDV and RVEDV during peak inspiration, peak expiration, end-inspiratory breath holding, and the Valsalva maneuver were compared with mean LVEDV and RVEDV during normal breathing.  $\$P < 0.05$  by repeated-measures ANOVA. B: short-axis image slices during peak inspiration (top left), peak expiration (top right), end-inspiratory breath holding (bottom left), and the Valsalva maneuver (bottom right). LV and RV endocardial contours were manually traced and presented as red and pink traces, respectively. From normal breathing to breath holding, RVEDV decreased slightly, whereas LVEDV remained the same. During the Valsalva maneuver, both RVEDV and LVEDV decreased significantly, with a more profound reduction for the RV.

LV ( $P = 0.045$  and  $P = 0.002$ , respectively). Both during breath holding and the Valsalva maneuver, LV SV was larger than RV SV ( $P = 0.021$  and  $P = 0.018$ , respectively).

#### *Exercise CMR Protocol*

As shown in Fig. 6, *A* and *B*, the effect of respiration on LV and RV volumes seen at rest was maintained throughout exercise. RVEDV and RVESV were significantly larger at peak inspiration compared with peak expiration ( $P < 0.0001$  and  $P = 0.001$ , respectively), resulting in greater peak-inspiratory RV SV throughout exercise ( $P = 0.01$ ). In contrast, LVEDV, LVESV, and LV SV were consistently larger during expiration throughout exercise ( $P < 0.0001$ ,  $P = 0.04$ , and  $P = 0.003$ , respectively). Similar to the respiratory maneuver protocol, LV EF and RV EF did not change with respiration, neither at rest nor during exercise ( $P = 0.81$  and  $P = 0.57$ , respectively).

Both at rest and during exercise, the diastolic eccentricity indexes were consistently greater at peak inspiration than at peak expiration (main effect:  $1.31 \pm 0.13$  vs.  $1.11 \pm 0.09$ ,  $P < 0.0001$ ), reflecting the greater inspiratory RV volume load. Similarly, the systolic eccentricity indexes were also consistently greater at peak inspiration (main effect:  $1.18 \pm 0.15$  vs.  $1.11 \pm 0.11$ ,  $P = 0.019$ ). Changes in the eccentricity index were greater at end diastole than at end systole (difference in main effects:  $0.19 \pm 0.11$  vs.  $0.07 \pm 0.11$ ,  $P = 0.001$ ). Figure 2 shows the changes in the eccentricity index with respiration.

#### DISCUSSION

Using the novel technique of real-time CMR, we have comprehensively described the influence of respiration on cardiac volumes in healthy subjects. The results of this study are in keeping with known physiology regarding the effect of respiration on LV SV. However, this study extends this knowledge to provide a far more complete description of the effect of respiration on both ventricles during multiple physiological states. For the first time, we simultaneously quantified both LV and RV volumes during free breathing, breath holding, and the Valsalva maneuver. Also, this is the first study in which the biventricular volume changes due to respiration were assessed during exercise. The results of this study indicate that respiration has a significant effect on both ventricles and should be taken into account when measuring biventricular volumes, both at rest and during exercise.

#### *Breathing Has a Differential Effect on Both Ventricles*

Multiple studies (5, 6, 16, 18, 20) have demonstrated that inspiration is associated with a reduction in LV SV. However, the mechanisms underpinning this phenomenon remain a point of conjecture and may include respiratory variations in afterload (6), transient inspiratory pooling of blood in the lungs (18), and alterations in LV compliance via diastolic ventricular interdependence (16). Recently, complex modeling has been used in an attempt to validate this concept of ventricular interaction (28). However, until present, the magnitude of the respiratory influence on simultaneous LV and RV volumes has not been quantified in healthy subjects, mainly due to limitations in imaging techniques to simultaneously capture LV and RV volumes. In a CMR study, Sigfridsson et al. (24) measured full LV volumes in one healthy subject throughout the entire

cardiac and respiratory cycle. Also, the authors assessed the effect of respiration on LV and RV diameters and reported an opposing effect on both ventricles (24).

In the present study, simultaneous volumetric measurements were obtained for both the LV and RV during respiration. This volumetric approach is important because the heart moves up and down in the thorax with respiration, which may result in through-plane motion. However, by delineating the endocardial borders consistently at the same point of the respiratory cycle for each slice level, either at peak inspiration or peak expiration, we could measure consistent and fully comparable biventricular volumes with the heart in different positions. Therefore, the observed volume changes in this study are due to the physiological effects of respiration and not due to translational errors in slicing. Inspiration resulted in a transient increase in RV volumes and a reciprocal decrease in LV volumes, whereas expiration caused the reciprocal changes. Thus, respiration caused a direct ventricular interaction whereby enhanced filling of one ventricle corresponded with reduced filling of the other (Figs. 1–3). We also demonstrated that the changes in LV filling were associated with an alteration in LV geometry. However, we cannot differentiate whether this was caused by a decrease in pressure in the LV associated with pooling of blood in the lungs (i.e., “suction effect”) or by an increase in RV pressure (i.e., “septal push”).

#### *Instantaneous LV and RV SV Are Not Equal*

Because the respiratory pump influences both ventricles differently, instantaneous LV and RV SV are not equal. However, in the absence of significant intra- or extracardiac shunts, LV and RV output should be approximately equal when averaged over time. More precisely, LV output should be slightly greater (~2%) owing to the normal physiological right-to-left shunt resulting from the left atrial drainage of the bronchial and Thebesian circulation (27). In this study, when SV was averaged over two time points in the cardiac cycle (peak inspiration and peak expiration), LV and RV SV were indeed similar during normal breathing at rest with, interestingly, a small excess in LV SV during exercise, perhaps suggesting that this technique is sufficiently accurate to measure the small physiological shunt that has only been measurable previously using more invasive techniques (27).

By comparing with end-inspiratory breath holding and the Valsalva maneuver, we demonstrated that respiration augments RV filling and SV. In addition, we observed a 25% decrease in LV SV during the Valsalva maneuver, which is very similar to the 20–30% drop in cardiac output during the Valsalva maneuver observed by Park et al. (15) using ungated spiral phase-contrast CMR imaging. However, in the latter study, RV volumes or pulmonary flow were not measured, such that the relative changes in LV versus RV SV during the Valsalva maneuver could not be compared. We observed a greater drop in RV SV relative to LV SV during end-inspiratory breath holding and the Valsalva maneuver. This may reflect the capacitance function of the RV and pulmonary circulation to buffer systemic venous return to keep LV SV relatively constant (4, 7, 19). Similarly, Aebischer et al. (1) found a greater decrease in RV than LV end-diastolic area during the Valsalva maneuver using echocardiography. The same authors also reported a sudden and dramatic increase in RV end-diastolic



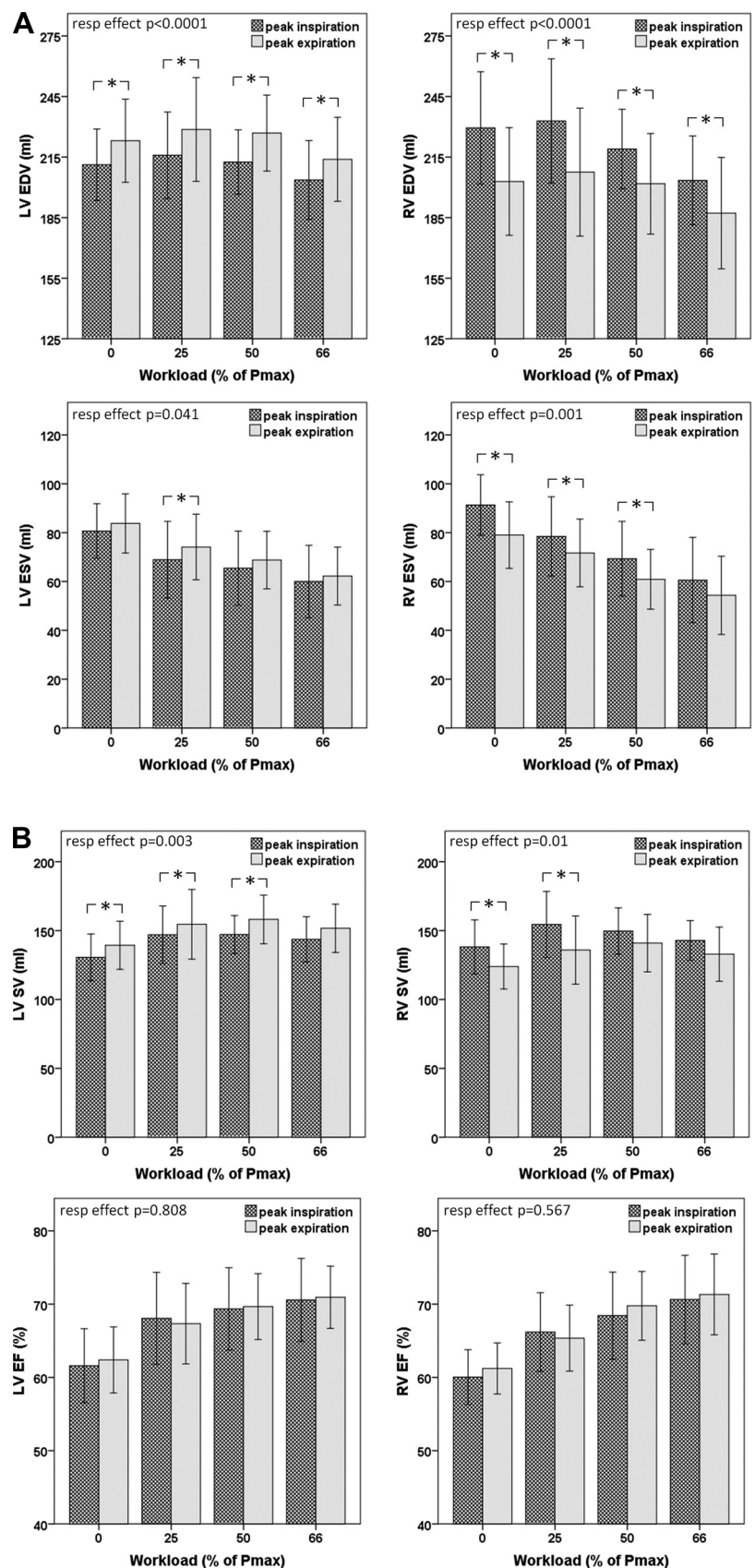


Fig. 6. Interaction between breathing and biventricular volumes during incremental exercise. A: EDV (top) and ESV (bottom); B: SV (top) and EF (bottom).  $P_{\max}$  is the maximum power wattage as determined on an upright cycle ergometer. Workloads are presented as a percentage of  $P_{\max}$ . \*Statistically significant differences between peak inspiration and peak expiration ( $P < 0.05$  by a paired samples  $t$ -test).  $P$  values are shown for the influence of breathing on LV and RV volumes as a within-subject effect ("resp effect").

area immediately after strain release, overshooting its baseline value, perhaps as a compensation for the transient mismatch in LV and RV SV during the Valsalva maneuver.

It is important to note the difference between the single end-inspiratory breath holds in the present study and conventional cine CMR imaging, which is typically performed during multiple breath holds in a relaxed state with an open glottis. In the latter setting, all image slices are acquired over multiple cardiac cycles such that LV and RV SV are effectively the average of volumetric data over many seconds. As a result, the respiratory phase differences in ventricular SVs are likely to be less than those we have identified using instantaneous measures. In clinical practice it is frequently assumed that the effect of respiration is negligible and SVs can be assumed to be equal, but this simplification of normal physiology has never been interrogated or validated. Our data demonstrate that respiration causes significant opposing changes in ventricular volumes. The extent to which measures acquired during breath holds approximate cardiac volumes during normal free-breathing physiology is yet to be tested.

#### *The Respiratory Pump Remains Active During Exercise*

Although the influence of breathing on LV and RV performance has been investigated previously at rest, there are very limited data on the interaction between the respiratory pump and both ventricles during exercise. This is largely due to difficulties in measuring rapid changes in absolute biventricular volumes with conventional imaging techniques, particularly during exercise. Recently, Boerrigter et al. (3) measured the respiratory variation in pulmonary artery pulse pressure, as a surrogate of breathing-induced changes in RV SV, during exercise in patients with chronic obstructive pulmonary disease and healthy subjects (3). Furthermore, other groups (8, 26) have used invasive or CMR-derived flow measures to quantify the effect of respiration on venous return and/or aortic flow during exercise. However, until the present study, no other studies have evaluated the direct influence of breathing on simultaneous LV and RV volumes during exercise. In the present study, we observed a consistent fluctuation of biventricular volumes and eccentricity indexes during all stages of exercise. These data confirm that the effects of the respiratory pump on LV and RV volumes are not only present at rest but persist to a similar degree during exercise.

#### *Clinical Implications*

With breath-hold cine CMR, image acquisition is typically performed over multiple cardiac cycles during several breath holds, with cardiac volumes estimated in either inspiration or expiration. Using this technique, investigators have assumed that SV in the two ventricles should be equal and have used this as a surrogate of accuracy (2, 12, 22, 28). However, we have demonstrated that instantaneous LV SV and RV SV are not equal. This may explain why some investigators have identified RV dominant cardiac morphology when images are acquired during inspiration (10), which contrasts with balanced morphology when similar cohorts have been examined during expiratory breath holds (21). Importantly, in this study, biventricular volumes were only assessed at peak inspiration and expiration, when the respiratory-induced volume changes were expected to be the most pronounced. Probably, the difference

between LV and RV SV in the intermediate phases of the respiratory cycle will be smaller. Hence, van den Hout et al. (25) demonstrated that respiratory-induced differences in LV SV increased with greater thoracic excursion. Also, in a previous study (9), we demonstrated that biventricular volumes were similar when measured consistently during early inspiration, defined as the onset of the upward deflection on the respiratory trace. Thus, the respiratory phase during which images are acquired should be considered in future studies in which cardiac volumes and morphology are evaluated.

The evaluation of the cardiorespiratory interaction is important in the setting of several cardiac pathologies. Our present data provides an insight into the hemodynamic mechanisms that increase LV SV during exercise with inspiratory unloading in patients with heart failure (11, 14). Furthermore, our methodology provides a tool capable of quantifying the effect of the respiratory pump and its contribution to cardiac output augmentation in patients with a single ventricle repair after congenital cardiac anomalies (23).

#### *Limitations*

Using ungated real-time CMR images, ~20 min is required to measure EDV and ESV for both ventricles at rest or at any given stage of exercise. Because of this manual and labor-intensive process, cardiac volumes were only measured at peak inspiration and expiration. However, as the heart rate is independent, it is impossible for end diastole and end systole to line up precisely with the respiratory cycle. We chose to select the end-diastolic phase that was closest to (but before) the maximal or minimal diaphragmatic excursion for peak inspiration and expiration, respectively, whereas the smallest blood pool area from the same cardiac cycle was selected as the end-systolic frame. Because the end-systolic frame usually fell just after the maximal or minimal diaphragmatic excursion, it is possible that rapid changes in intrathoracic pressures immediately before and after peak inspiration and expiration may have influenced EDV and ESV differently. Therefore, a frame-to-frame analysis, i.e., measuring all intermediate phases of the cardiac and respiratory cycles, would have been most complete. However, at present, this approach would be far too time consuming. The development of automated segmentation and contour detection software may potentially reduce postprocessing times, which would enable biventricular volumes to be assessed throughout the respiratory cycle.

A second limitation of this study was that individual variations in performance of breath holding or the Valsalva maneuver may have influenced the cardiovascular response. However, measurement of the respiratory excursion with a plethysmograph and visual inspection of the diaphragmatic motion during image acquisition allowed real-time assessment of the quality of the respiratory maneuvers in each subject.

#### *Conclusions*

Ventricular volumes oscillate with respiratory phase such that RV and LV volumes are maximal at peak inspiration and expiration, respectively. Thus, interpretation of RV versus LV volumes requires careful definition of the exact respiratory time point for proper interpretation, both at rest and during exercise.



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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

## AUTHOR CONTRIBUTIONS

Author contributions: G.C., A.L.G., and H.H. conception and design of research; G.C., J.B., and A.L.G. performed experiments; G.C. and A.L.G. analyzed data; G.C., P.C., M.D., J.B., A.L.G., and H.H. interpreted results of experiments; G.C. and A.L.G. prepared figures; G.C. and A.L.G. drafted manuscript; G.C., P.C., M.D., J.B., A.L.G., and H.H. edited and revised manuscript; G.C., P.C., M.D., J.B., A.L.G., and H.H. approved final version of manuscript.

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